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Step-Economical Access to Valuable Weinreb Amide 2,5-Disubstituted Pyrrolidines by a Sequential One-Pot Two-Directional Cross-Metathesis/Cyclizing Aza-Michael Process

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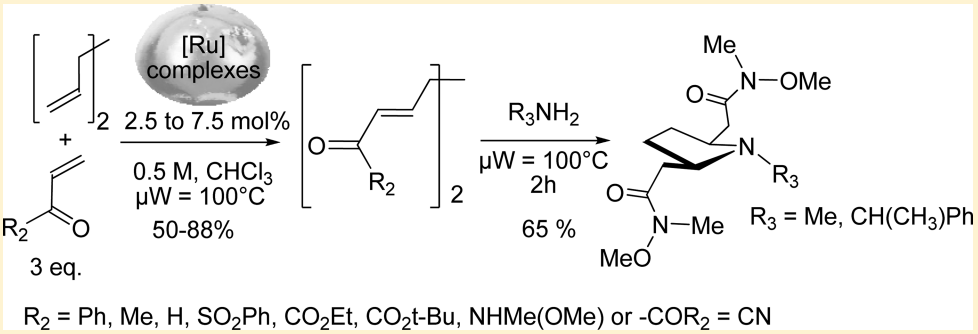
Supporting Information



ABSTRACT: Double cross-metathesis of 1,5-hexadiene with a variety of electron-deficient alkenes including the reluctant Weinreb acrylamide has been successfully accomplished. It was found that the process is quite general, and microwave irradiation effectively accelerates cross-coupling metathesis. This promotes a very versatile and high yielding methodology for the synthesis of symmetric Michael acceptors, which can be transformed into 2,5-disubstituted pyrrolidines through a sequential one-pot two-directional cross-metathesis/ring-closing double aza-Michael process.

INTRODUCTION

As the stereochemistry of chiral drugs controls their pharmacokinetic, pharmacodynamic, and toxicological actions, the development of products containing the pure and therapeutically active isomer is become crucial. *Meso*-compounds can serve as an efficient means for not only directly circumventing the constraint of marketing single enantiomers (i.e., varenicline) but also, through their desymmetrization, for generating usefully functionalized enantioenriched building blocks with potential application in the asymmetric synthesis of biologically active products, allowing multiple stereocenters to be created in a single symmetry-breaking transformation.[1] In this context, we have had, over the past few years, an ongoing interest in the development of a step-economical synthetic process of valuable *meso*-2,5-disubstitued pyrrolidines **1** with potential application as ligands of nicotinic acetylcholine receptor subtypes.[2] The shortness and the flexibility of their synthetic pathway are ensured by a two-directional Wittig olefination followed by a stereoselective tandem ring-closing double aza-Michael reaction (RCDAM) (Scheme 1).

It is currently well-known that these strategies that combine a two-directional approach for building simple symmetrical functionalized chains with tandem reactions to "fold" these chains both offer the potential to reduce the number of operations and are able to create elaborated complex cyclic scaffolds and stereocenters.[3] Nevertheless, preparation of the pivotal bis-Michael electrophile **2** by two-directional Wittig olefination had drawbacks: reaction is carried out from the short-lived succinaldehyde **3** stemming from diene oxidative cleavage, and triphenylphosphine oxide is produced as byproduct, both in the reduction of ozonide and in the Wittig homologation, rendering the procedure poorly atom-economical.[2,4]

With the emergence of more active and more stable ruthenium-based precatalysts, olefin metathesis has benefited from some improvements in terms of selectivity, efficiency, and functional group tolerance.[5] Therefore, the formation of carbon−carbon bonds by olefin metathesis became one of the most powerful and broadly applicable synthetic tools of modern chemistry.[6] Consequently, in order to reach in a short sequence the molecularly diversified bis-enones **2**, two-

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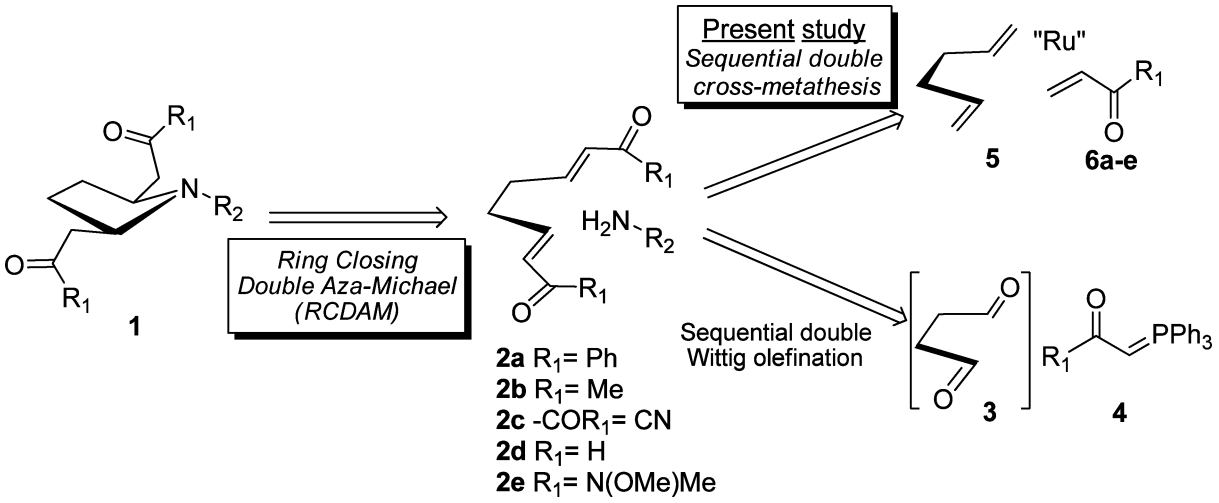
Scheme 1. Two Principal Direct Accesses to Pyrrolidines 1 from Bis-enones 2: Preceding and Present Studies



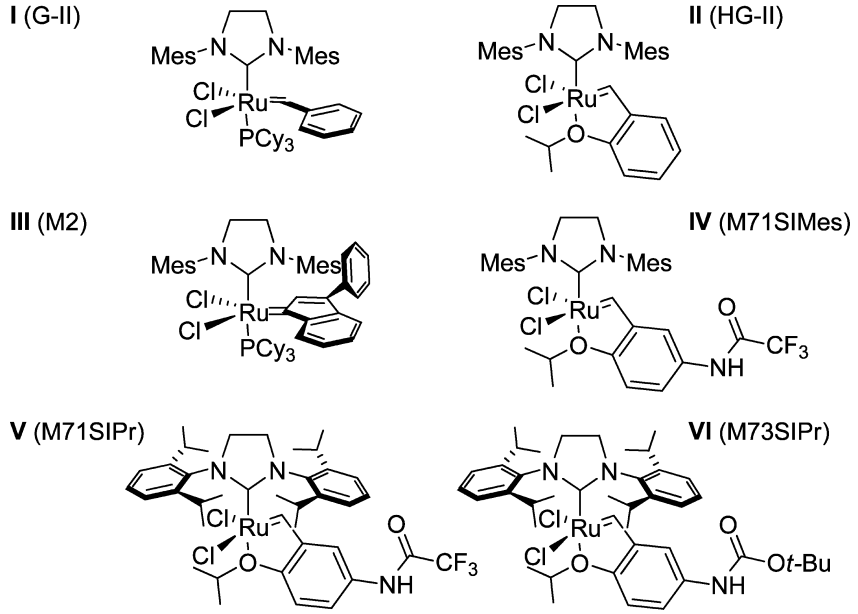


Figure 1. Selected available ruthenium-based metathesis complexes.[15]

directional olefin CM appears to be the method of choice, offering advantages over a more traditional Wittig route by virtue of minimizing the amount of hazardous reagents (Scheme 1). Moreover, Fustero and co-workers recently reported the synthesis of pyrrolidines and piperidines through a domino CM/aza-Michael strategy.[7]

Although CM promoted by ruthenium complexes have been widely utilized by organic as well as polymer chemists in the construction of higher olefins from simple alkene precursors, two-directional chain homologation by double CM reaction is not so common in the literature.[5a,8] For instance, in 2001, Cossy and co-workers reported the double cross-metathesis between the dissymmetric hexa-1,5-dien-3-ol and acrolein, offering the double homologated dialdehyde in 70% yield and high *E*/*E* stereoselectivity.[9] In 2008, Gouverneur et al. described the efficient double CM of the C_2-symmetric hexa-1,5-diene-1,4-diol with an excess of allyltrimethysilane.[10] More recently Stockman developed a two-directional CM that offers a high-yielding method of doubly homologating substituted α,ω-alkenes by a variety of electron-deficient alkenes to give exclusively the *E*,*E*-dienes.[3b,11] However, to the best of our knowledge, no example of two-directional homologation by CM starting from volatile unfunctionalized olefin such as the 1,5-hexadiene **5** has been described. Indeed, less volatile cyclic alkenes are preferred as potential long-chain precursors through ring-opening metathesis-double cross-metathesis (ROM-CM);[12a] hence, 1,5-cyclooctadiene (COD) may be used as substrate in preference to 1,5-hexadiene. Nevertheless, ROM-CM of COD in the presence of electron-poor acrylates was very sluggish[12a] or usually yielded end-functionalized dimers.[12b]

Consequently, two-directional CM of the 1,5-hexadiene **5** becomes particularly challenging when Weinreb acrylamide is used as the electron-deficient alkene partner in the CM. Indeed, although Weinreb amides are widely used as effective acylating reagents, allowing the direct preparation of highly functionalized aldehydes or ketones,[13] the Weinreb acrylamide **6e** has been rarely used in CM and never in double homologating CM. Recently, it was shown that only the Grubbs–Hoveyda second generation catalyst (**II**, Figure 1) was able to catalyze, in slow rates and low yields (<36%), the CM of allyl halides with the

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Weinreb acrylamide **6e**.[14] With the aim of elaborating new pyrrolidine scaffolds based upon Weinreb amide functionality, we describe herein our successful use of a set of available ruthenium-based complexes in the two-directional homologating CM of volatile 1,5-hexadiene **5** with deactivated Weinreb acrylamide **6e** (Scheme 1).

RESULTS AND DISCUSSION

We first investigated the efficiency of six available Ru complexes[15] (Figure 1) regarding the CM between 1,5-hexadiene **5** and reluctant Weinreb acrylamide **6e**. These precatalysts were chosen taking into account their catalytic features: (i) three standard metathesis complexes such as the Grubbs second generation **I** (G-II),[16a] the Grubbs–Hoveyda second generation **II** (HG-II),[16b] and the indenylidene-based complex **III** (M2)[16c] (Figure 1); (ii) three well-defined fast-initiation Hoveyda-type complexes bearing either a SIMes (**IV**) or a SIPr (**V**-**VI**) NHC unit (Figure 1).[17]

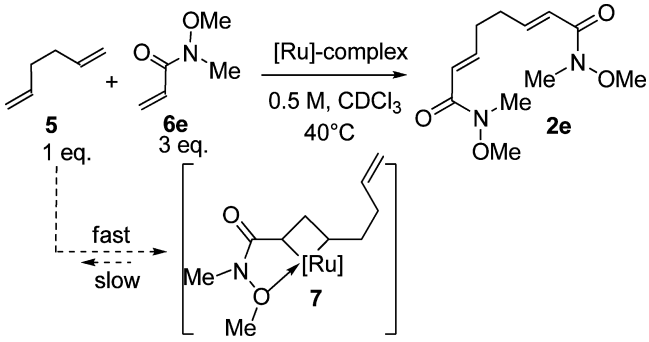
Reactions were carried out at 40 °C in deuterated chloroform using an excess of Weinreb acrylamide, which was prepared in 65% yield according to a one-step published procedure (Table 1).[18] We started the screening of complexes with the Grubbs complex **I** at 5 mol % of catalyst loading.[19] After 3 h of reaction, 45% of conversion of the desired *E*,*E*-diene **2e** (monitored by ^{1}H NMR spectroscopy) was observed (Table 1; entry 1). An additional time of reaction (3 h) led to the same conversion, attesting that the major part of the catalyst was deactivated during the first 3 h of reaction. The achievable formation of the corresponding stable five-membered cyclic intermediate **7** could explain the sluggish reaction rates (Table 1).[14a]

Interestingly, through the sequential addition of **I** in two portions of 2.5 mol %, at the reaction start and then 6 h later, the metathesis product **2e** was formed in 83% conversion after 24 h (Table 1; entry 2). We then decided to compare all precatalysts using the beneficial sequential addition of Ru-complex. Pleasingly, for all of them, CM reactions were highly stereoselective, affording exclusively the symmetric *E*,*E*-diene **2e** without any trace of either mono- or self-metathesis byproducts. However, as depicted in Figure 2, their reactivity profiles were quite distinct. The HG-II catalyst **II** showed a slower reactivity after 6 h (40%, Table 1; entry 3) but reached the same conversion after 24 h (81%). Despite a poor induction period (only 35% after 3 h, Table 1; entry 4), the M2 complex **III** appeared to be the more efficient catalyst, producing the dihomologated product **2e** in 95% of conversion after 24 h.

Curiously, regarding electronically modified Hoveyda precatalysts **IV**, **V**, and **VI**, we were disappointed to observe lower or similar kinetic profiles in comparison with standard Hoveyda–Grubbs complex **II** (Table 1; entries 5–7). In addition, the double metathesis transformation remained incomplete after 24 h of reaction, reaching 80% of conversion in best cases (Table 1; entry 7). The poor induction observed within the first 3 h with these fast-initiating complexes could be attributed to the rapid formation of the unproductive intermediate **7** (Table 1). Pleasingly, these opening results tend to prove that difunctionalizing CM with the Weinreb acrylamide **6e**, as a well-known CM bad partner, is attainable and reproducible with satisfactory conversion.

We then pursued our study by evaluating the effect of various solvents on the CM using precatalyst **III**, which initially gave the highest conversion to the desired double Michael acceptor **2e** (Table 1). Conversions were determined after 24 h of reaction time, and the results are summarized in Figure 3.

Table 1. Two-Directionnal CM with Weinreb Acrylamide and 1,5-Hexadiene



entry	Ru-complex (mol %)	time (h)	conv (%)[c]
1	**I** (5)[a]	3	43
		6	43
		24	50
2	**I** (2 × 2.5)[b]	3	62
		6	65
		24	81
3	**II** (2 × 2.5)[b]	3	40
		6	40
		24	81
4	**III** (2 × 2.5)[b]	3	35 (15)[d]
		6	46 (30)[d]
		24	95 (75)[d]
5	**IV** (2 × 2.5)[b]	3	12
		6	24
		24	65
6	**V** (2 × 2.5)[b]	3	50
		6	55
		24	60
7	**VI** (2 × 2.5)[b]	3	52
		6	70
		24	80

[a]Reaction was performed at 40 °C in $CDCl_3$ (0.5M) with 5 mol % catalyst. [b]Reaction was performed at 40 °C in $CDCl_3$ (0.5M) with 2.5 mol % catalyst; after 6 h of reaction, another amount of catalyst (2.5 mol %) was added. [c]Monitored by ^{1}H NMR spectroscopy. [d]Reaction was performed in a sealed tube in refluxing $CDCl_3$ (0.5 M) with 2.5 mol % catalyst; after 6 h of reaction, another amount of catalyst (2.5 mol %) was added.

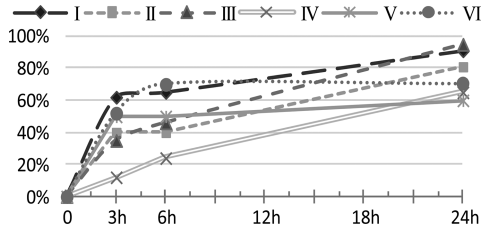


Figure 2. Kinetic profiles of double CM of diene **5** and Weinreb acrylamide **6e** with 2 × 2.5 mol % of catalysts **I**–**VI** at 40 °C in $CHCl_3$ (0.5 M). The conversions were monitored by ^{1}H NMR spectroscopy.

Changing the solvent to dichloromethane, the customary solvent for Ru-catalyzed olefin metathesis, had no significant impact, while a dramatic influence was noted when toluene was used, reaching only 58% of conversion. Interestingly, hexafluorobenzene was recently shown to give impressive results even in difficult metathesis reactions.[16c,20] Nonetheless, the rate of conversion to **2e** remained less important than in

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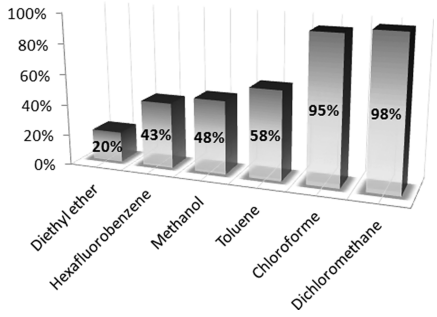


Figure 3. Solvent screening for the CM of diene **5** and acrylamide **6e** catalyzed by **III** after 24 h reaction time (standardized conditions as denoted in Table 1).

toluene (43%).[21] In addition, in order to disfavor the formation and the stabilization of the intermediate **7** through intermolecular interaction with polar and more particularly with protic solvents, we evaluated their influence on our model reaction of double CM. In methanol, a moderate conversion (48%) similar to those observed in C_6F_6 was obtained, and diethyl ether induced a dramatic loss of conversion (20%). These results demonstrated that the desired two-directional homologating CM of Weinreb acrylamide with the catalyst **III** occurred in high yield in dichlormethane or in chloroforme, suggesting that, in this solvent type, the lifetime of the active catalytic species is prolonged.

In order to accelerate this CM, we pursued by studying the effect of the temperature. The reaction was performed in a sealed tube using a classical oil-bath heating, and in refluxing chloroform-d_1, the reaction conversions were lesser (Table 1; entry 4) showing that prolonged heating accelerated the precatalyst degradation. In recent years, microwave (μW) irradiation has been proposed as a complementary activation mode for olefin metathesis, resulting in many cases in a spectacular reaction time shortening.[22] Therefore, we have studied the profile of the double CM reaction at 100 °C in $CDCl_3$ in a sealed vessel heated under microwave irradiation (200 W). The protocol for the sequential addition of precatalysts has been slightly modified: 2.5 mol % was introduced at the beginning and then a second similar portion after 1 h of reaction. As depicted in Table 2 and Figure 4, the

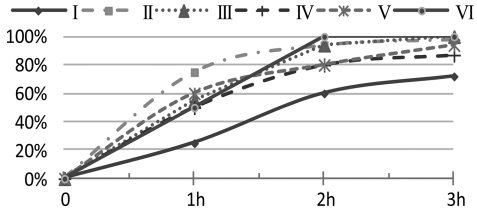
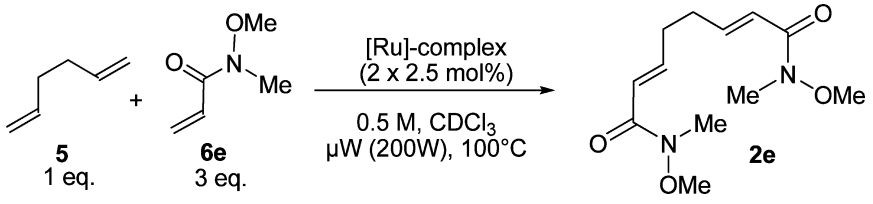


Figure 4. Reaction profiles of double CM of diene **5** and Weinreb acrylamide **6e** with 2 × 2.5 mol % of catalysts **I**–**VI** under μW irradiation in $CDCl_3$ (0.5M). The conversions were determined by ^{1}H NMR spectroscopy.

benefit of μW was significant as the diene **5** was totally converted into the double acceptor **2e** after only 3 h with indenylidene complex **III** (Table 2; entry 3). Similarly, after 3 h, the CM reaction was complete with the Hoveyda–Grubbs **II**, while 72%, 87%, and 94% conversion were reached with complexes **I**, **IV**, and **V** respectively (Table 2; entries 1, 2, 4, 5). To our delight, only 2 h were necessary to ensure complete two-directional homologation of the diene with the precatalyst **VI** (Table 2; entry 6). The additional benefit of microwave

Table 2. Double CM with Weinreb Acrylamide and 1,5-Hexadiene under Microwave Irradiation (200 W, 100°C)



entry	catalyst	time (h)	conv (%)[a]
1	**I** (G-II)	1	25
		2	60
		3	72
2	**II** (HG-II)	1	75
		2	94
		3	100
3	**III** (M2)	1	55
		2	94
		3	100
4	**IV** (M71SIMes)	1	50
		2	80
		3	87
5	**V** (M71SIPr)	1	60
		2	80
		3	94
6	**VI** (M73SIPr)	1	50
		2	100
		3	

[a]Determined by ^{1}H NMR spectroscopy.

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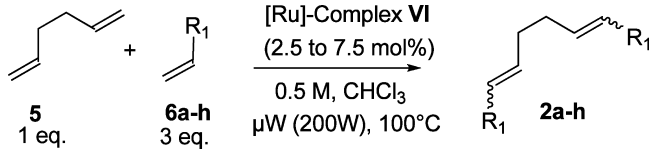
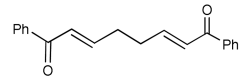
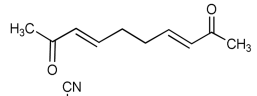
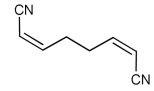
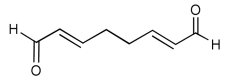
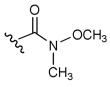
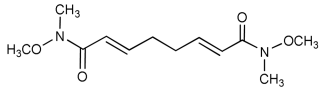
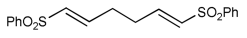
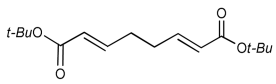
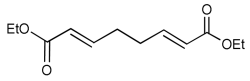
Table 3. Substrate Scope for Microwave-Assisted CM Reactions with the 1,5-Hexadiene 5 in the Presence of the Catalyst VI



Entry	Substrate **6** R_1	Catalyst **VI** (mol%)[a]	Time (h)[e]	Isolated yield (%)	Product **2**
1	**6a** 	2.5	1	70	**2a** 
2	**6b** 	2.5	1	85	**2b** 
3	**6c** 	4 x 1[b]	4	55	**2c** 
4	**6d** 	4 x 1[c]	2.5	50	**2d** 
5	**6e** 	2 x 2.5[d]	2	88	**2e** 
6	**6f** 	3 x 2.5[d]	2.5	55	**2f** 
7	**6g** 	2.5	1	88	**2g** 
8[b]	**6h** 	2.5	1	75	**2h** 

[a]Reaction conditions: 0.5 M chloroforme solution of 1,5-hexadiene **5** (1 equiv), olefin partner **6** (3 equiv), and the precatalyst **VI** (2.5−7.5 mol %) was heated with stirring to 100 °C under μW irradiation (200 W). [b]1 mol % of precatalyst **VI** was added every hour. [c]1 mol % of precatalyst **VI** was added each half-hour. [d]2.5 mol % of precatalyst **VI** was added every hour. [e]The consumption of 1,5-hexadiene **5** was monitored by ^{1}H NMR spectroscopy.

irradiation in terms of reaction rates is clearly demonstrated in practically all cases tested, and delightfully, the excellent *E*/*E*-diastereoselectivity is conserved. We believe that an important contribution of microwaves in this reaction may result in an increase of reaction rate before the catalysts' decomposition.

In summary, we have evaluated and compared the catalytic performance of some Ru-based metathesis precatalysts: it appears that most of the selected commercially available Ru-complexes are effective to obtain dihomologated diene **2e** under variable conditions. Microwave irradiation clearly allows fast, clean, and efficient double CM reaction of the Weinreb amide **6e** with Ru-complex **VI**.

Scope of the Two-Directional Cross-Metathesis of 1,5-Hexadiene. As metathesis reactions are strongly substrate-dependent, the substrate scope and the versatility of this methodology were examined under the preeminent reaction conditions. Various Michael acceptors with terminal olefins were engaged in the CM with 1,5-hexadiene catalyzed by the complex **VI**, and the reaction was performed in chloroform at 100 °C under microwave activation. Results are summarized in Table 3.

Very satisfyingly, most of symmetrical double Michael acceptors **2** were isolated with the exclusive *E*/*E*-selectivity showing the excellent diastereoselectivity of this CM catalyzed by **VI**. In contrast, the cross-metathesis product **2c** was obtained as the sole (*Z*,*Z*)-stereoisomer, which is consistent with earlier observations for acrylonitrile CM.[23] According to the substituent nature of the olefin partner **6**, catalyst loading and sequential addition of precatalyst **VI** had to be adapted and optimized in order to maintain good yields. The CM of the phenyl and methyl vinyl ketones **6a** and **6b** afforded the double homologated dienes **2a** and **2b** in 70% and 85% isolated yield, respectively, within 1 h with only 2.5 mol % of catalyst loading (Table 3; entries 1 and 2). Similarly, the alkyl acrylate **6g** and **6h** were found to be very efficient substrates for the double CM, requiring only 2.5 mol % of **VI** and 1h of reaction, even in the presence of the bulky *tert*-butyl ester group (Table 3; entries 7 and 8). The phenyl vinyl sulfone **6f** appeared more reluctant as a large amount of **VI** (7.5 mol %) and a prolonged reaction time were necessary to afford the metathesis product **2f** in moderate 55% isolated yield (Table 3; entry 6). In the same way, the double CM using acrylonitrile **6c** and acroleine **6d** required improvements, but still modest yields were attained when 1 mol % of **VI** was sequentially and regularly (every hour or 30 min) added (Table 3; entries 3 and 4). With the electrophilic alkenes **6c−d,f**, the yield erosion should find a first explanation in the particular instability of the bis-olefination products **2c−d,f** under chromatographic purification conditions. Additionally, with the olefins **6d** and **6f**, the formation of 10% of self-metathesis byproducts has been observed by ^{1}H NMR spectroscopy of the crude mixture. In the particular case of the acrylonitrile **6c**, one also recognized that it possessed an ability to deactivate or degrade the catalyst.

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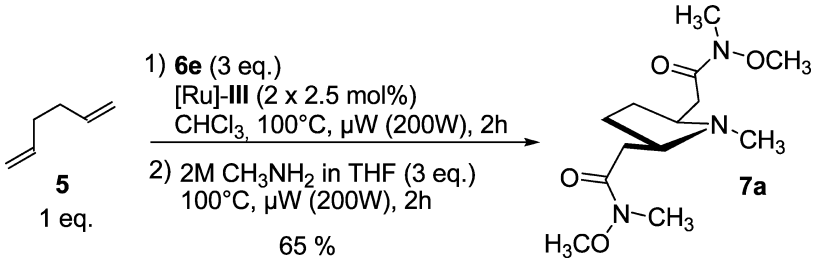
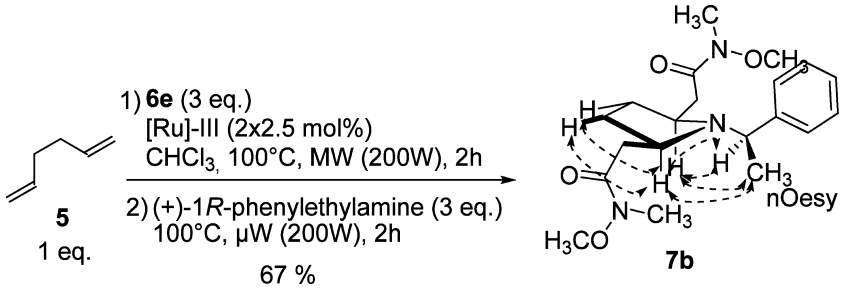
Scheme 2. Synthesis of 2,5-Disubstitued Pyrrolidines by Sequential Tandem Double CM/RCDAM Reaction



Scheme 3. Synthesis of Enantiopure 2,5-Disubstitued Pyrrolidine 7b by Sequential Tandem Double CM/RCDAM Reaction and Its Relative Configuration Determined by NOESY Experiments



One-Pot Sequential Two-Directional Cross-Metathesis–Cyclizing Double Aza-Michael Process. Complementarily, as CM offers the advantages over a more traditional Wittig route by virtue of minimizing the step number and developing more eco-compatible viable processes, the sequential cascade of double CM/RCDAM was studied. Earlier, Fustero showed that a combination of a Lewis acid and a ruthenium-based catalyst was required to undergo the CM/aza-Michael cascade process to yield pyrrolidines and piperidines.[7] In our case, the double CM between the 1,5-hexadiene **5** and the Weinreb acrylamide **6e** under microwave irradiation in the presence of the complex **III** (or **VI**), followed by the sequential addition of methylamine (3 equiv), led to the new pyrrolidine **7a** in excellent 65% yield over two steps (Scheme 2). Moreover acrylamide and acrylate substituted in the β-position generally constituted a bad partner in the aza-Michael addition and required an unconventional activation mode.[2a] The efficiency of this tandem sequence double CM/RCDAM can be explained by the activation of the α,β-unsaturated amide by a ruthenium intermediate, which can act as a Lewis acid.

In order to unambiguously determine the relative configuration of the pyrrolidine amide arms, the enantiopure pyrrolidine **7b** was diastereoselectively synthesized by the same strategy using the enantiopure (+)-1*R*-phenylethylamine instead of the methylamine (Scheme 3).

In virtue of two-dimensional NOESY correlations, the *syn* configuration of the amide arms and their *anti* configuration in relation to the nitrogen substituent are confirmed (Scheme 3 and Supporting Information). Indeed, as previously described,[2] only one conformer is characterized due to the absence of free rotation around the bond between stereogenic carbon and the pyrrolidine nitrogen. By consequence, in the unique rotamer, the chemically equivalent ^{1}H and ^{13}C in the cyclic compound become magnetically different. The RCDAM addition of chiral primary amines under thermal condition gives the unique thermodynamic *syn*-product. That can find an explanation in the reversibility of the AM addition.

CONCLUSION

In conclusion, we have developed an efficient and step-economical access to symmetric double Michael acceptors by the first two-directional homologating double CM of the unfunctionalized 1,5-hexadiene. We have evaluated a selection of six Ru-precatalysts and clearly demonstrated that most of them were able to provide in good conversions (up to 95%) and excellent selectivity the expected bis-homologated *E,E*-diene **2e** from Weinreb acrylamide **6e** but in due reaction time. Compared to conventional heating, the highly beneficial effect of microwave irradiation was evidenced, allowing dramatic reduction of reaction times and ensuring a fast metathesis reaction relative to catalyst decomposition. This methodology was successfully extended to other electron-withdrawing olefin partners, affording corresponding bis-functionalized *E,E*-diene **2** in moderate to good isolated yields. In addition, this methodological study was then applied to the synthesis of 2,5-*cis* disubstituted pyrrolidines through a one-pot sequential tandem double CM/RCDAM reaction affording a valuable pyrrolidine *Lobelia* alkaloid precursor.

EXPERIMENTAL SECTION

Commercially available reagents were used throughout without further purification other than those detailed below. Prior to use, THF and toluene were dried by means of a SP-1 Stand Alone Solvent Purification System apparatus. All anhydrous reactions were carried out under argon atmosphere. Microwave experiments were carried out in a CEM Discover Labmate microwave oven using 10-mL pressurized vials. Temperature measurements of microwave experiments were done by external infrared fiber optic probe. Analytical thin layer chromatography was performed on silica gel 60F-254 precoated plates (0.2 mm) on glass and was revealed by UV light or Kägi-Misher or Dragendorf reagent. Flash chromatography separations were performed on silica gel (40–63 μm) or on neutral activated aluminiumoxid 90 (63–200 μm). Infrared (IR) spectra were obtained as neat films. ^{1}H and ^{13}C NMR spectra were recorded on apparatus respectively at 300 or 400 MHz and 75 or 100 MHz, respectively, unless otherwise specified. The chemical shifts for ^{1}H NMR were recorded in ppm downfield from tetramethylsilane (TMS) with the

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solvent resonance as the internal standard. Coupling constants (J) are reported in hertz and refer to apparent peak multiplications. NMR peak assignments have been made on the basis of HMBC, HMQC, NOESY, and ^{1}H−^{1}H COSY spectra. The electrospray impact (ESI) and the atmospheric pressure chemical ionization (APCI) mass spectra were realized on a spectrometer. Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. High resolution mass spectroscopy (HRMS) was performed using a Q-TOF instrument with leucine-enkephalin as accurate mass reference. Diastereomeric excesses (de) were evaluated by ^{1}H NMR spectroscopy. Specific rotations $[\alpha]^{20}_D$ were measured with sodium (589 nm) lamp at 20 °C in a 1-dm cell and were given in units of 10^{-1} deg cm^2 g^{-1}, and concentrations are quoted in grams per 100 mL.

***N*-Methoxy-*N*-methyl-acrylamide (6e).**[18] The desired product has been prepared according to the published procedure in a similar yield. Yellowish oil (4.25 g, 74% yield) (purified by flash chromatography/cyclohexane/EtOAc 2:1); IR ν_{max}/cm^{-1} 1659 (C═O), 1620 (C═C), 1460 (C−N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (1H, dd, J = 17.1 and 10.3 Hz), 6.28 (1H, dd, J = 17.1 and 2.0 Hz), 5.61 (1H, dd, J = 10.3 and 2.0 Hz), 3.58 (3H, s), 3.12 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (C═O), 128.5 (CH_2), 125.6 (CH), 61.4 (CH_3), 31.9 (CH_3). The data presented above are in agreement with those detailed in the literature.[18]

Typical Procedures for Two-Directional Homologating CM. *Procedure a (Classical Oil-Bath Heating).* To a stirred solution (0.5 M) of 1,5-hexadiene **5** (37 μL; 0.305 mmol) in appropriate solvent (0.6 mL) was added consecutively olefin **6** (3 equiv, 0.915 mmol) and catalyst (2.5 mol %; see Table 1) under an argon atmosphere. The solution was oil-bath heated at 40 °C for 6 h. After cooling to room temperature, an additional amount of catalyst (2.5 mol %; see Table 1) was introduced, and the reaction mixture was heated in the same conditions for 18 h more. After cooling to room temperature, the reaction mixture was concentrated under vacuum, and the residue was purified by flash column chromatography to afford the corresponding bis-homologated compound **2**.

Procedure b (Microwave Heating). A microwave vial was filled with olefin **5** (37 μL; 0.305 mmol) and deactivated olefin partner **6** (3 equiv, 0.915 mmol) in chloroform (0.6 mL), before the addition of precatalyst (from 1 to 2.5 mol %; see Tables 2 and 3). The vial was sealed, and the mixture was heated with stirring to 100 °C using microwave irradiation (200 W) for the reported time (see Tables 2 and 3). The internal pressure depended upon the head space of the vial (typically 2.0 bar). According to the starting deactivated olefin partner **6**, additional amounts of precatalyst (from 2.5 to 5 mol %; see Tables 2 and 3) were sequentially introduced every hour or 30 min. After cooling to room temperature, the vial content was then transferred to a round-bottom flask, and the solvent was removed under reduced pressure. The crude was subsequently purified via flash chromatography under silica gel using the appropriate eluent to obtain the analytical pure product.

(2*E*,6*E*)-1,8-Diphenylocta-2,6-diene-1,8-dione (2a).[4e] Yellowish solid (62 mg, 70% yield) (purified by flash chromatography, cyclohexane/EtOAc 3:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (4H, d, J = 7.3 Hz), 7.55 (2H, t, J = 7.4 Hz), 7.45 (4H, t, J = 7.7 Hz), 7.04 (2H, m), 6.93 (2H, d, J = 15.7 Hz), 2.57 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4 (Cq), 147.2 (CH), 137.7 (Cq), 132.7 (CH), 128.5 (CH), 128.5 (CH), 126.8 (CH), 31.2 (CH_2). The data presented above is in agreement with that detailed in the literature.[4e]

(3*E*,7*E*)-Deca-3,7-dien-2,9-dione[24] **(2b).** Colorless oil (43 mg, 85% yield) (purified by flash chromatography, cyclohexane/EtOAc 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (2H, m), 6.09 (2H, d, J = 15.9 Hz), 2.40 (4H, m), 2.23 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1 (Cq), 145.8 (CH), 131.8 (CH), 30.5 (CH_3), 27.2 (CH_2). The data presented above is in agreement with that detailed in the literature.[24]

(2*Z*,6*Z*)-Octa-2,6-dienedinitrile (2c). Yellowish oil (22 mg, 55% yield) (purified by flash chromatography, cyclohexane/EtOAc 9:1); IR (neat) ν (cm^{-1}) 2221, 1620, 1447, 1308, 1261, 1146, 1086; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (2H, m), 5.42 (2H, d, J = 10.8 Hz), 2.63 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4 (C≡N), 151.7 (CH), 115.4 (Cq), 101.6 (CH), 30.1 (CH_2). Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.63; H, 6.25; N, 21.12.

(2*E*,6*E*)-Octa-2,6-dienedial (2d). Yellowish oil (21 mg, 50% yield) (purified by flash chromatography, cyclohexane/EtOAc 4:1); IR (neat) ν (cm^{-1}) 1671, 1623, 1260, 975; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (2H, d, J = 7.5 Hz), 6.82 (2H, m), 6.17 (4H, dd, J = 15.5 and 7.5 Hz), 2.59 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4 (Cq), 155.1 (CH), 133.8 (CH), 30.5 (CH_2); HRMS calcd for $C_8H_{10}O_2$ ([M + H]$^+$) 139.0760, found 139.0759.

(2*E*,6*E*)-*N*-Methoxy-*N*-methyl-octa-2,6-dienediamide (2e). Yellowish oil (69 mg, 88% yield) (purified by flash chromatography, cyclohexane/EtOAc 1:1 − EtOAc); IR (neat) ν (cm^{-1}) 2341, 1661, 1437, 1385, 1178, 1119; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (2H, m), 6.32 (2H, d, J = 15.5 Hz), 3.57 (6H, s), 3.09 (6H, s), 2.30 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (Cq), 145.2 (CH), 119.4 (CH), 61.3 (CH_3), 31.9 (CH_3), 30.6 (CH_2); HRMS calcd for $C_{12}H_{20}N_2O_4$ ([M + H]$^+$) 257.1497, found 257.1501.

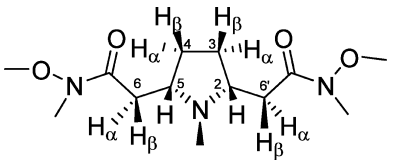
(1*E*,5*E*)-1,6-Bis(phenylsulfonyl)hexa-1,5-diene (2f). Brown oil (61 mg, 55% yield) (purified by flash chromatography, cyclohexane/EtOAc 3:1); IR (neat) ν (cm^{-1}) 1620, 1447, 1319, 1306, 1143, 1085; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (4H, d, J = 7.1 Hz), 7.63 (2H, t, J = 7.5 Hz), 7.50 (4H, t, J = 7.6 Hz), 6.90 (2H, m), 6.35 (2H, d, J = 15.0 Hz), 2.40 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8 (CH), 140.1 (Cq), 133.4 (CH), 132.0 (CH), 129.3 (CH), 127.5 (CH), 29.3 (CH_2); HRMS Calcd for $C_{18}H_{18}O_4S_2$ ([M + H]$^+$) 363.0725, found 363.0720.

(2*E*,6*E*)-Octa-2,6-diendioic Acid Di-*tert*-butyl Diester[25] **(2g).** Colorless solid (75 mg, 88% yield) (purified by flash chromatography, cyclohexane/EtOAc 4:1); mp 67−68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (2H, m), 5.75 (2H, d, J = 15.5 Hz), 2.31 (4H, m) 1.46 (18H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2 (Cq), 145.2 (CH), 123.4 (CH), 114.9 (CH), 79.7 (Cq), 29.9 (CH_2), 27.6 (CH_3). Physicochemical data are in agreement with literature.[25]

(2*E*,6*E*)-Octa-2,6-diendioic Acid Diethyl Diester[26] **(2h).** Colorless oil (103 mg, 76% yield) (purified by flash chromatography, cyclohexane/EtOAc 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (2H, dt, J = 15.6 and 6.2 Hz), 5.85 (2H, d, J = 15.6 Hz), 4.18 (4H, q, J = 7.1 Hz), 2.37 (4H, m), 1.28 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (Cq), 147.0 (CH), 122.1 (CH), 60.3 (CH_2), 30.5 (CH_2), 14.3 (CH_3). Physicochemical data are in agreement with literature.[26]

Typical Procedure for Tandem Double CM/RCDAM Reaction. To a stirred solution of the 1,5-hexadiene **5** (74 μL; 0.61 mmol) in $CHCl_3$ (0.5 M; 1.2 mL) were added consecutively the Weinreb acrylamide **6e** (3 equiv, 1.83 mmol) and catalyst **III** (2.5 mol %). The vial was sealed, and the mixture was heated with stirring to 100 °C using microwaves irradiation (200 W) for 1h. After another addition of 2.5 mol % of catalyst, the mixture was heated for an additional hour. After cooling, primary amine (3 equiv, 1.83 mmol) was then added, and the mixture was heated with stirring to 100 °C using microwaves irradiation (200 W) for 2 h. The crude solution was then filtered and evaporated under reduced pressure. The crude was subsequently purified via flash chromatography on neutral alumina.

2-[1-Methyl-5-(2-*N*-methoxy-*N*-methylamide)-pyrrolidin-2-yl]-*N*-methoxy-*N*-methylacetamide (7a).



The reaction was carried out using a 2 M solution of methylamine in THF. Yellowish oil (113 mg, 65% yield) (purified by flash chromatography, EtOAc); IR (neat) ν (cm^{-1}) 1654, 1638, 1462, 1411, 1385, 1175; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (6H, s), 3.17 (6H, s), 2.78 (4H, m, $H_{6\alpha}$–$H_{6'\alpha}$–H_2–H_5), 2.43 (2H, m, $H_{6\beta}$–$H_{6'\beta}$), 2.30 (3H, s), 2.06 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 1.46 (2H, m, $H_{3\alpha}$–$H_{4\alpha}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (C═O), 63.1 (CH), 61.1 (CH_3), 39.0 (CH_3), 36.7 (CH_2), 31.9 (CH_3), 29.6 (CH_2). Low resolution

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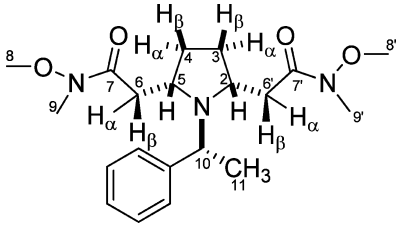
mass spectroscopy (CI): *m*/*z* (%) 288 (100); HRMS calcd for $C_{13}H_{25}N_3O_4$ ($[M + H]^+$) 288.1922, found 288.1923.

(−)-2-[1-(1*R*-Phenylethyl)-5-(2-*N*-methoxy-*N*-methylamide)-pyrrolidin-2-yl]-*N*-methoxy-*N*-methylacetamide (7b).



The reaction was carried out starting from 1-(*R*)-phenylethylamine. Yellow oil (154 mg, 67% yield) (purified by flash chromatography, EtOAc); de ≥ 95%; $[\alpha]^{20}_D$ −8° (*c* 0.02 in $CHCl_3$); IR (neat) ν (cm^{-1}) 1649, 1535, 1492, 1384; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40 (2H, d, *J* = 7.4 Hz, *o*-H_{Ar}), 7.29 (2H, t, *J* = 7.4 Hz, *m*-H_{Ar}), 7.20 (1H, t, *J* = 7.2 Hz, *p*-H_{Ar}), 4.01 (1H, m, H_{10}), 3.64 (3H, s, H_8), 3.56 (1H, m, H_5), 3.49 (3H, s, $H_{8'}$), 3.48 (1H, m, H_2), 3.15 (3H, s, H_9), 3.08 (3H, s, $H_{9'}$), 2.65 (1H, m, $H_{6\alpha}$), 2.45 (1H, m, $H_{6'\alpha}$), 2.25 (2H, m, $H_{6\beta}$, $H_{6'\beta}$), 1.90 (1H, m, $H_{3\beta}$), 1.80 (1H, m, $H_{4\beta}$), 1.56 (1H, m, $H_{3\alpha}$), 1.53 (1H, m, $H_{4\alpha}$), 1.45 (3H, d, *J* = 6.4 Hz, H_{11}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, (C_7, $C_{7'}$), 144.1 (C_{12}), 128.1 (*o*,*m*-CH_{ar}), 126.8 (*p*-CH_{ar}), 61.2 (C_8), 61.0 ($C_{8'}$), 58.6 (C_5), 58.5 (C_{10}), 56.4 (C_2), 40.1 ($C_{6'}$), 39.8 (C_6), 32.0 (C_9), 30.9 ($C_{9'}$), 30.9 (C_3), 30.4 (C_4), 15.8 (C_{11}); HRMS calcd for $C_{20}H_{31}N_3O_4$ ($[M + H]^+$) 378.2393, found 378.2393.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of the compounds **2c−f**, **6e**, and **7a,b** and HMBC, HMQC, and NOESY NMR spectra of compound **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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